Docket PHO-122

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	)
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Dees et al.	)
	)
Serial No.: 09/900,355	)
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Filed: July 6, 2001	)
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For: Medicaments For Chemotherapeutic Treatment of Disease	)
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	)
Examiner: J. Epps Ford	)
	)
Confirmation No.: 5998	)
	)
Art Unit: 1635	)

DECLARATION OF PETER HERSEY

I, Dr. Peter Hersey, FRACP, D.Phil., hereby declare the following:

1) I am Dr. Peter Hersey of 172 Russell Road, New Lambton Heights, NSW 2305 Australia.

2) I have been employed by the Newcastle Mater Misericordiae Hospital, Newcastle, NSW Australia, since 1984 as Senior Staff Specialist in Immunology and Oncology. I have served as Conjoint Professor of Oncology at the University of Newcastle since 1985, and am the Medical and Research Director of the Newcastle Melanoma Unit. I have also been a member of the WHO Committee on Melanoma since 1992. In these capacities, I have been active in both research and clinical practice in oncology, including development and use of chemotherapeutic, radiosensitizer, and immunotherapy medicaments for treatment of melanoma and other cancers.

3) I have the following relevant qualifications and experience:

- Awarded 8 prizes for Distinction in Surgery, Medicine, Obstetrics and Gynaecology

- D.Phil. (Oxon) Thesis 1973, "Immunological mechanisms in tumour rejection"
- Hold membership in the following societies:
  - Australian Society for Immunology
  - American Association of Immunologists
  - American Association for Cancer Research
  - Clinical Oncology Society of Australia
  - Medical Oncology Group
  - Fellow Royal Australian College of Physicians (FRACP)
  - The Society for Biological Therapy
- My research group is recognized as an international leader in (a) apoptosis of melanoma, including mechanisms of induction by the immune system and resistance mechanisms to apoptosis induced by the immune system and by chemotherapy, and in (b) immunotherapy of melanoma. In both fields our work has been at the forefront of new developments and has helped to establish new trends in research.
- For the past 20 years, I have played a leading role in the development of new drugs for melanoma. The clinical trial of vaccinia melanoma cell lysate vaccine as adjuvant treatment for melanoma has been the largest randomized trial of vaccines so far reported. I was the first investigator in Australia to conduct trials of alpha-interferon (IFN-α) in patients with melanoma, and was the first (internationally) to treat patients with Interleukin-2. Since 2000, I have participated in a number of international trials and have been invited to serve on the Medical Advisory Committees for trials by several major international pharmaceutical companies. Additionally, I have served as Principal Investigator for the Newcastle Melanoma Unit on over 15 clinical trials.

4) I have read U.S patent application number 09/900,355 and the pending claims of 12 February 2007, the Final Rejection thereof from the U.S. Patent and Trademark Office dated 4 May 2007, and the prior art relied upon by the Examiner therein (Heitz et al., U.S. Patent 4,846,789), along with the section of the Colour Index referenced in Heitz.

5) I understand that the U.S. Patent and Trademark Office considers that the claimed halogenated xanthenes, specifically, 4,5,6,7-Tetrabromoerythrosin, Monobromo-erythrosin, Dibromoerythrosin and Tribromoerythrosin, are obvious in light of the disclosure of Heitz. I disagree and believe that others skilled in the art would also disagree.

6) In my opinion, whereas Hetiz states that certain "derivatives of fluorescein (C.I. No. 45350) having one or more substituents in the 4, 5, 6, 7, 2', 4', 5' and 7' positions selected from the group consisting of F, Cl, Br, I, –NO2, –COOH and –OH are especially important" (col. 4, lines 22-27), such disclosure does not render the claimed invention of this application obvious for at least several reasons. I note that this section in Heitz references the Colour Index (C.I.).

7) Firstly, the claimed halogenated xanthenes of this application require substitution of fluorescein at the 2', 4', 5' and 7' positions with 4 atoms of iodine and at the 4, 5, 6 and 7 positions with 1 to 4 atoms of bromine. No such compounds are represented in the Colour Index or Heitz, and, in fact, of the large number of compound listed in the Colour Index, only five have 5 or more halogens at any of these positions, and none of these contain both iodine and bromine. Thus, the Colour Index and Heitz do not disclose any of the claimed compounds or any closely related compounds.

8) Secondly, the claimed compounds are the result of a highly specific pattern of chemical substitution. Such a specific pattern of substation is not the result of routine experimentation. The claimed compounds are the result of highly specialized starting materials and have been combined in a very specific way to result in the claimed specific compounds. For instance, synthesis of 4,5,6,7-Tetrabromoerythrosin would presumably require condensation of resorcinol with tetrabromophthalic anhydride, followed by iodination of the resulting intermediate with I_2. Since tetrabromophthalic anhydride is not a standard compound, this crucial starting material itself would require custom synthesis. Hence, the claimed compounds could not result from random experimentation.

9) In fact, other than blind luck, the only way I believe one could arrive at the claimed compounds is through use of the disclosure in the inventors' patent application. If one was using the disclosure in Heitz, there appears to be over 5 million possible combinations of the cited substituents in the eight positions 4, 5, 6, 7, 2', 4', 5' and 7'. Other than by luck, it would take many lifetimes for one skilled in the art to use the disclosure in Heitz and arrive at any of the claimed compounds through random experimentation.

10) Thirdly, Heitz provides no motivation for one of skill in the art to synthesize the claimed compounds. Heitz's disclosure is predicated on use of *known photoactive compounds*, such as those listed in the Colour Index, for pesticidal purposes in livestock. Since the claimed compounds were unknown at the time of Heitz, and since Applicants' claimed use (chemotherapeutic medicaments for use in humans) is distinctly different from that of Heitz, it would not be obvious to one of skill in the art to create the new compositions of matter represented by Applicants' claimed compounds for an entirely new application as delineated by the Applicants.

11) Finally, whereas Heitz describes certain uses of known photoactive compounds for pesticidal purposes in livestock, such disclosure would not motivate one of skill in the art to use such known compounds, and especially would not motivate one to create the new compounds claimed by the inventors, for the chemotherapeutic uses claimed in this application. I have been actively engaged in the development of new therapeutic modalities, methods, and medicaments for the treatment of cancer for over thirty years. Throughout this time, I have been aware of many uses for a number of the compounds cited by Heitz, including Fluorescein, Rose Bengal, and Eosin. Despite this knowledge, I would never have conceived of, nor was I aware of anyone else conceiving until this invention, using any halogenated xanthene as a chemotherapeutic agent. Prior to the discoveries discussed in this application, such compounds were universally considered to be inert in the absence of irradiation with light. Thus, the teachings of Heitz, alone or in combination with any other prior art, would not have motivated me to discover or develop the claimed chemotherapeutic uses and medicaments. Nor would they have led me to the novel halogenated

xanthenes (i.e., 4,5,6,7-Tetrabromoerythrosin, Monobromoerythrosin, Dibromo-erythrosin and Tribromoerythrosin) that are the subject of the claimed invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued.

Peter Hersey

Dr. Peter Hersey

Date: 20/6/07